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Potential Impact of Metabolic Syndrome Control on Cardiovascular Risk in Elderly Patients with Diabetes: A Cross-Sectional Study

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Potential Impact of Metabolic Syndrome Control on Cardiovascular Risk in Elderly Patients with Diabetes: A Cross-Sectional Study

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Abstract: Metabolic syndrome (MS), a complex pathology with features like abnormal body fat distribution, insulin resistance, and dyslipidaemia, contributes to higher cardiovascular (CV) risk. A cross-sectional study including 87 individuals, assessed CV risk in elderly patients with type 2 diabetes and MS in Algarve, Portugal. The 10-year CV risk was estimated using the ADVANCE risk score calculator. The reductions in CV risk were estimated by adjusting the data inputted on the online tool to achieve systolic blood pressure (SBP) <130 or <120 mmHg, and LDL-cholesterol <70 mg/dL. Beyond waist circumference, the mean number of clinical features of MS was 3.14±0.84, without significant sex differences. The mean CV risk was 22.5% (CI: 20.3-24.7). Sex-specific analysis showed higher risk in males (24.2%, CI: 21.3-27.0) vs. females (19.7%, CI: 16.2-23.3; p=0.028). Hypothetical risk reductions show that lowering SBP to <130 mmHg could significantly lower the risk by an average of 9.2% (CI: 7.7-10.7), whereas 34.5% of the participants would be out of the diagnostic criteria for MS. When comparing each potential intervention with current risk, all interventions significantly reduce the 10-years CV risk. The study highlights the potential of blood pressure control in reducing CV risk and the importance of multifaceted risk reduction strategies.

Keywords: cardiovascular risk; ADVANCE risk score calculator; metabolic syndrome; type 2 diabetes mellitus; elderly

1. Introduction

Metabolic syndrome (MS) is defined by the International Diabetes Federation (IDF) as a complex pathology characterized by several general features, such as abnormal body fat distribution, insulin resistance, atherogenic dyslipidaemia, proinflammatory state and prothrombotic state [1]. Persistent insulin resistance often leads to the development of type 2 diabetes *mellitus* (T2DM), a metabolic disease characterized by chronic hyperglycaemia, due to an impaired capacity of the utilization of glucose as an energy source, along with impaired gluconeogenesis and glycogenolysis [2,3]. This can lead to both micro and macrovascular complications in the long term. Microvascular complications include retinopathy (leading to total vision loss), neuropathy (leading to impaired wound healing and amputations in the lower limbs), nephropathy (possible renal failure), and sexual dysfunction (namely erectile dysfunction in men) [4]. Macrovascular complications include peripheral and coronary artery disease, arrhythmias, diabetic cardiomyopathy, and cerebrovascular disease. Cardiovascular diseases are the leading cause of death in patients with T2DM [5,6].

Ageing of the population is a global phenomenon and Portugal is one of the European countries experiencing a considerable increase in the proportion of elderly people (i.e., individuals aged 65 and over). Ageing index, which measures the ratio of the elderly to the young population, has seen an exponential rise over the years, reaching 185.3% in 2022 [7]. This demographic shift led to an increase

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in age-related diseases, including metabolic disorders such as T2DM [8]. In this context, it becomes relevant to invest in the prevention of possible complications arising from metabolic syndrome.

Currently, several tools are available to assess cardiovascular (CV) risk [9–11]. These tools consider various factors that can contribute to increased CV risk, including the presence of diabetes, blood pressure levels, LDL-cholesterol levels, age, sex, smoking status, prescribed medications, and the presence of complications. These tools show several advantages, such as a personalized risk assessment and a guidance to clinical decision related to the need of lifestyle modifications or the prescription of medication. However, they also have limitations, namely variable accuracy because they are based on average population data. Also, these tools may lead to over-reliance and do not consider all risk factors, such as family history or genetic markers.

The ADVANCE calculator evaluates the CV risk in T2DM patients diagnosed with metabolic syndrome [12]. This tool is a specific calculator to assess the 10-year risk of suffering a cardiovascular event, for patients with diabetes. Using this calculator, we aimed to estimate how reducing systolic blood pressure and/or LDL-cholesterol until the recommended levels could decrease the CV risk and potentially revert the metabolic syndrome diagnosis in elderly patients.

2. Materials and Methods

2.1. Characteristics of the Study

A descriptive cross-sectional study was conducted to assess CV risk in elderly patients with T2DM and MS. The study analysed a non-random convenience sample of 87 patients, residing in the Algarve region (Southern Portugal), aged between 65 and 86 years old, diagnosed with MS according to the IDF criteria [1]. Patients were recruited at the diabetes clinic of the Association for the Study of Diabetes Mellitus and Support for Diabetics in the Algarve (AEDMADA, according to the Portuguese designation), by direct invitation at the time of their consultations for diabetes monitoring. All patients signed an informed consent for their data to be used in this study.

2.2. Data Collection

Clinical data were extracted from the patients' clinical files, which included sociodemographic characteristics (age, sex, education level), lifestyle factors (exercise frequency, and tobacco and alcohol consumption), clinical profiles (hypertension, dyslipidaemia, duration of diabetes), complications from diabetes (retinopathy, nephropathy, neuropathy), cardiometabolic parameters (weight, body mass index (BMI), waist circumference, systolic and diastolic blood pressure), biochemical parameters (fasting glucose, HbA1c, albumin, creatinine, and cholesterol levels), and the total number of medications used by each patient. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), moderate obesity (30-34.9 kg/m^2), severe obesity (35-39.9 kg/m^2), and very severe obesity (≥40 kg/m^2) [13].

2.3. Cardiovascular Risk Calculations and Estimations

The 10-year CV risk was estimated using the ADVANCE risk score calculator [12], an online tool specifically designed for patients with diabetes. This tool also provides estimates on risk reduction achievable through specific adjustments in systolic blood pressure (SBP) and LDL cholesterol levels. Missing data points for the time of diabetes diagnosis and albumin/creatinine ratio were filled with mean population values whenever data were not available.

The reductions in CV risk were estimated by adjusting the data inputted on the online tool to achieve SBP either below 130 mmHg or 120 mmHg, and lowering LDL cholesterol below 70 mg/dL. These reductions were based on the recommendations from the American Diabetes Association (ADA). The impact of combined adjustments of SBP (<120 mmHg) and LDL cholesterol (<70 mg/dL) was also analysed. Although ADA proposes that blood pressure target values should be individualized, target values of SBP <130 mmHg should be considered whenever possible [14]. Nevertheless, reducing SBP below 120 mmHg was also considered as it may benefit cardiovascular risk [15,16].

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The possibility of starting antiplatelet therapy was not considered in the potential interventions, as the information for this in-depth analysis of the clinical history was not available.

2.4. Statistical Analysis

Data were described using absolute and relative frequencies, mean (M), median (Md), standard deviation (SD) and interquartile range (IQR). We used the Kolmogorov-Smirnov test to assess adherence to the Normal distribution. Group comparisons were made using Pearson chi-square, Mann-Whitney, and Student's t-test, according to the results of the normality test. When the results of the chi-square test were considered non-valid due to low expected frequency count, Fisher's or Fisher-Freeman-Halton's exact tests were computed. Correlations were computed using Spearman's correlation coefficient and paired sample comparison were made using the Wilcoxon's rank test.

Statistical significance for all procedures was set at 0.05. All analyses were carried out using IBM SPSS Statistics 29.0.

3. Results

3.1. Sociodemographic Characteristics of the Population and Metabolic Syndrome Diagnosis

To assess the CV risk in elderly patients with T2DM, 87 patients (62% males; n=54) aged 65 years or more were included in this study. The mean age was 75±5 years, without significant differences between the sexes (*p=0.133*) (Table 1). Regarding the academic level, most participants had completed elementary school (67.8%), followed by middle school (14.9%), and high school (6.9%). Only 4.6% of the participants completed a higher degree course. The mean time since the T2DM diagnosis was 13±8 years. On average, patients were taking 6±3 medicines. Table 1 presents the demographic, clinical and lifestyle characteristics of the participants.

Table 1. Sociodemographic, clinical and lifestyle characteristics for all participants and by sex.

Characteristics		Total sample (*n*=87)		Males (*n*=54)		Females (*n*=33)		*p*-value
Age (years) M±SD		71.6	±5.2	70.8	±4.8	72.8	±5.6	0.113[a]
Academic level:	Cannot read or write; n (%)	5	(5.7)	3	(5.6)	2	(6.1)	0.697[b]
	Primary school (4 years); n (%)	59	(67.8)	33	(61.1)	26	(78.8)	
	Middle school (5-9 years); n (%)	13	(14.9)	10	(18.5)	3	(9.1)	
	High school (10-12 years); n (%)	6	(6.9)	5	(9.3)	1	(3.0)	
	College level degree; n (%)	4	(4.6)	3	(5.6)	1	(3.0)	
Years after T2DM diagnosis	M±SD	12.9	±8.0	12.5	±8.2	13.5	±7.7	0.371[a]
Number of medications	M±SD	6	.0±2.9	5.7	±2.8	6	.5±3.0	0.240[a]
Weight (Kg)	M±SD	80.6	±11.8	83.8	±10.0	75.4	±12.9	**0.001**[c]
Waist circumference (cm)	M±SD	96.8	±8.3	99.7	±5.1	92.0	±10.2	**<0.001**[a]
BMI (kg/m²)	M±SD	29.8	±3.9	29.1	±2.7	31	.0±5.2	0.07[c]
BMI (category):	Normal weight; n (%)	5	(5.7)	1	(1.9)	4	(12.1)	**0.008**[b]
	Overweight; n (%)	45	(51.7)	33	(61.1)	12	(36.4)	
	Moderate obesity; n (%)	28	(32.2)	18	(33.3)	10	(30.3)	
	Severe obesity; n (%)	7	(8.0)	2	(3.7)	5	(15.2)	
	Very severe obesity; n (%)	2	(2.3)		0	2	(6.1)	
Systolic BP (mmHg)	M±SD	153.6	±22.4	153	±22.6	154.5	±22.7	0.776[c]
Diastolic BP (mmHg)	M±SD	80.4	±11.0	79.5	±10.3	81.8	±12.0	0.349[c]
Total cholesterol (mg/dL)	M±SD	184.3	±37.8	180.2	±36.8	191	±39.1	0.195[a]
HDL cholesterol (mg/dL)	M±SD	46.5	±12.0	45.4	±12.5	48.4	±11.2	0.261[a]
LDL cholesterol (mg/dL)	M±SD	106.9	±27.6	105.1	±26.6	109.9	±29.5	0.441[a]
Triglycerides (mg/dL)	M±SD	143.5	±57.2	146.1	±56.7	139.4	±58.6	0.47[a]
HbA1c (%)	M±SD	8.3	±1.1	8.1	±1.0	8.6	±1.2	0.072[a]

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Fasting glycaemia (mg/dL)	M±SD	164.7	±45.4	165.6	±51.4	163.2	±33.9	0.726[a]
Smokes tobacco	n (%)	2	(2.3)	2	(3.7)		0	**<0.001**[d]
Drinks alcohol	n (%)	59	(67.8)	47	(87.0)	12	(36.4)	**<0.001**[d]
Exercises regularly	n (%)	53	(60.9)	34	(63.0)	19	(57.6)	0.656[b]
Hypertension	n (%)	79	(90.8)	50	(92.6)	29	(87.9)	0.471[f]
Dyslipidaemia	n (%)	49	(56.3)	31	(57.4)	18	(54.5)	0.827[b]
Retinopathy	n (%)	27	(31.0)	16	(29.6)	11	(33.3)	0.812[b]
Neuropathy	n (%)	2	(2.3)	2	(3.7)		0	0.524[f]
Nephropathy	n (%)	3	(3.4)	2	(3.7)	1	(3.0)	0.680[d]

M – mean; SD – standard deviation; BMI – body mass index; BP – blood pressure; Gender differences computed with: [a] – Mann-Whitney's test; [b] - chi-square test; [c] – Student's t-test; [d] – Fisher-Freeman-Halton exact test; [f] – Fisher's exact test; Statistical significance (p<0.05) is **boldfaced**.

The anthropometric variables were significantly different between the sexes (Table 1). Males had a higher body weight (83.8±10 kg) compared to females (75.4±12.9 kg; *p<0.001*), and a larger abdominal circumference (100±5 cm for males vs. 92±10 cm for females; *p<0.001*). Overall mean BMI was 29.8±3.9 kg/m^2. Even if the differences in average BMI were not statistically significant between sex (*p=0.07*), the BMI classification shows a higher prevalence of men with a BMI above the normal range (*p=0.008*).

Significant sex differences were also observed in tobacco and alcohol consumption (Table 1). Only males reported smoking (3.7%), and a higher percentage of males reported alcohol consumption (87.0%) compared to females (36.4%) (*p<0.001*). Regular exercise was reported by 60.9% of the total sample, without significant sex differences (*p=0.656*).

Clinical parameters such as systolic and diastolic blood pressure, cholesterol levels, triglycerides, HbA1c, and fasting glycaemia showed no significant differences between the sexes. The prevalence of clinical conditions such as high blood pressure, dyslipidaemia, retinopathy, neuropathy, and nephropathy also did not differ significantly according to sex.

To determine whether the patients gathered the required components of MS, specific clinical and biochemical characteristics were considered (Table 2). According to the IDF criteria, MS diagnosis includes central obesity (waist circumference ≥94 cm for males, and ≥80 cm for females) plus any two of the following four factors: elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glycemia [1]. In addition to the increased waist circumference (Table 1), the mean number of clinical features identified in the participants was 3.14±0.84 (Table 2). There were no significant differences between sexes in the number of characteristics or in the prevalence of any of the MS characteristics.

Table 2. Prevalence of metabolic syndrome (MS) characteristics for all participants and by sex.

Metabolic syndrome characteristics	Total sample (*n*=87)	Males (*n*=54)	Females (*n*=33)	*p*-value
BMI showing obesity; n (%)	37 (42.5)	20 (37.0)	17 (51.5)	0.264[a]
Triglycerides ≥ 150 mg/dL; *n* (%)	35 (40.2)	23 (42.6)	12 (36.4)	0.655[a]
HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; *n* (%)	38 (43.7)	19 (35.2)	19 (57.6)	**0.040**[a]
Blood pressure ≥ 130/85 mmHg	78 (89.7)	48 (88.9)	30 (90.9)	1[a]
Fasting glucose ≥ 100 mg/dL	85 (97.7)	52 (96.3)	33 (100)	0.524[b]
No. of clinical features for MS diagnosis in addition to increased waist circumference:				
M±SD	3.1±0.8	3.0±0.7	3.4±1.0	
Md (IQR)	3.0 (1.0)	3.0 (0.0)	3.0 (1.0)	0.109[c]

M – mean; SD – standard deviation; Md – Median; IQT – interquartile range; Gender differences computed with: [a] – chi-square test; [b] – Fisher's exact test; [c] – Mann-Whitney's test; Statistical significance (p<0.05) is **boldfaced**.

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3.2. Calculation of the ADVANCE Risk Score

The ADVANCE risk score is a CV disease risk prediction tool specifically developed for patients with T2DM, which takes into consideration diabetes-specific variables [17]. The estimated risk percentages for myocardial infarction, stroke, or vascular death over a 10-year period, were calculated using the ADVANCE risk score online tool (Table 3). The mean risk for all participants was 22.5% (CI: 20.3-24.7). Sex-specific analysis shows a significantly higher current risk in males (24.2%, CI: 21.3-27.0) compared to females (19.7%, CI: 16.2-23.3) (*p=0.028*).

Table 3. Risk for myocardial infarction, stroke or vascular death in the next 10 years, and potential interventions.

Risk for myocardial infarction, stroke or vascular death in the next 10 years (%)	**ADVANCE risk score** Mean (95% confidence interval)			**Sex differences** *p*-value
	Total sample (*n*=87)	**Males** (*n*=54)	**Females** (*n*=33)	
Current risk	22.5 (20.3-24.7)	24.2 (21.3-27)	19.7 (16.2-23.3)	**0.028**
Risk if SBP <130 mm Hg *	13.4 (11.8-15.1)	14.6 (12.4-16.8)	11.7 (9.1-14.4)	0.061
Risk if SBP <120 mm Hg *,**	11.8 (10.3-13.3)	13.0 (11.1-14.9)	9.8 (7.6-11.9)	**0.024**
Risk if LDL cholesterol <70 mg/dL *	18.8 (16.6-20.9)	20.3 (17.6-23.1)	16.3 (12.9-19.8)	**0.026**
Risk if SBP <120 mmHg & LDLC <70 mg/dL *	9.7 (8.4-11.0)	10.8 (9.1-12.6)	7.9 (6.1-9.7)	**0.013**

SBP – systolic blood pressure; LDLC- LDL cholesterol; Gender differences computed with Mann-Whitney's test; * – Paired comparison with current risk are statistically significant (**p<0.001**) for all participants, males, and females; ** - Paired comparison with BP <130 mm Hg is statistically significant (**p<0.001**) for all participants, males, and females; Risk comparisons between interventions computed with Wilcoxon's rank test; Statistical significance (p<0.05) is **boldfaced**.

Potential risk reductions show that lowering systolic BP to levels below 130 mmHg could lower the risk by an average of 9.2% (CI: 7.7-10.7), placing it at 13.4% (CI: 11.8-15.1) for the total sample. This potential risk after the intervention is statistically significant (*p<0.001*) when compared to current risk (22.5%), albeit it does not show significant differences between the sexes (*p=0.061*). By contrast, sex differences are observed in potential interventions that succeed in either lowering systolic BP below 120 mmHg (*p=0.024*), lowering LDL cholesterol below 70 mg/dL (*p=0.026*), and lowering both systolic BP below 120 mmHg and LDL cholesterol below 70 mg/dL (*p=0.013*) (Table 3). Thus, males seem to maintain a higher risk than females, except when the intervention is more conservative (systolic BP <130 mm Hg).

When comparing each potential intervention with current risk, all interventions significantly reduce the risk for myocardial infarction, stroke, or vascular death in the next 10 years (*p<0.001*). Nevertheless, mean risk reduction is not significantly different between sexes when considering all potential interventions.

As expected, the most substantial risk reduction is observed when combining both BP and LDL cholesterol interventions, which places overall risk at 9.7% (CI: 8.4-11.0) for the total sample, at 10.8% (CI: 9.1-12.6) for males, and at 7.9% (CI: 6.1-9.7) for females. This intervention yields statistically significant decreases from the current baseline (*p<0.001*, with an overall decrease of 12.7%, CI: 9.4-14.3), placing males at a higher risk than females (*p=0.013*). Nevertheless, the risk decrease is not statistically different between males and females (*p=0.512*): 13.3% (CI: 9.2-15.2) for males and 11.8% (CI: 6.7-15.1) for females.

The calculated current risk for myocardial infarction, stroke, or vascular death in the next 10 years shows a positive correlation with both age (r=0.728, *p<0.001*) and time since T2DM diagnosis (r=0.681, *p<0.001*), when controlling for sex. This suggests that older patients and those who have a longer duration of the disease have a higher risk for these events. Also, when controlling for sex, risk reduction still shows important significant correlations: risk reduction given when BP<130 mmHg is positively correlated with age (r=0.411, *p=0.003*) and time since T2DM diagnosis (r=0.425, *p=0.002*); risk reduction given when BP<120 mmHg is also positively correlated with age (r=0.510, *p<0.001*) and

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time since the diagnosis (r=0.503, *p<0.001*); risk reduction given when LDL cholesterol<70 mg/dL is positively correlated with time since the T2DM diagnosis (r=0.319, *p=0.024*), but not with age (r=0.197, *p=0.171*). Our results suggest that older patients can benefit more from BP control, but not necessarily from reducing LDL cholesterol levels. Patients who have longer duration of T2DM benefit from interventions favouring lower BP and LDL cholesterol. According to our data, an effective intervention that lowers BP<130 mmHg in our sample would result in 34.5% of participants (n=30) being outside the diagnostic criteria for MS.

4. Discussion

Given the higher susceptibility of elderly adults to cardiovascular (CV) diseases and their associated complications, it is crucial to identify and address modifiable risk factors to mitigate these health concerns. The current study examined a cohort of Portuguese elderly individuals diagnosed with both type 2 diabetes and metabolic syndrome, to estimate their CV risk and determine suitable clinical targets, i.e., key modifiable factors such hypertension and dyslipidaemia, to reduce the calculated risk.

As individuals age (a non-modifiable factor), the prevalence of type 2 diabetes tends to increase. In Portugal, diabetes affects over a quarter of the population aged 60-79 years, showing a greater prevalence in males [18]. According to data from the Portuguese population survey, around one fifth of the general population and more than half of the elderly (aged 65 and over) have only four years of schooling [19]. This low academic level agrees with the studied sample, which suggests that this sample can be considered representative of the elderly Portuguese population.

Our study demonstrates that aggressive blood pressure (BP) control, particularly lowering systolic BP below 120 mmHg, can substantially and significantly reduce the estimated 10-year cardiovascular risk for all participants. Lowering blood pressure to <130 mmHg also seems to have a significant impact on reducing 10-years CV risk. Considering the risks associated with more aggressive control (<120 mmHg) in patients with diabetes, this study shows that even the values recommended by the ADA [14] and the European Society of Cardiology [20] for blood pressure control (<130 mmHg) may have beneficial effects in reducing cardiovascular risk. More importantly, the combined effect of BP and LDL cholesterol interventions yields the most significant risk reduction. Our findings emphasize the potential benefits of multifaceted intervention strategies targeting both BP and lipid levels to mitigate cardiovascular risk in patients with diabetes and metabolic syndrome already reported in other studies [20].

The ADA recommends the use of the American College of Cardiology/American Heart Association ASCVD risk calculator to calculate 10-year cardiovascular risk. However, it states that although this calculator includes diabetes as a risk factor, it does not consider the duration of the disease or the presence of long-term complications [14]. The tool used in this study (ADVANCE) includes both factors in the calculation of cardiovascular risk [12] and seems to be a good tool to help guide the therapy and goals of individuals with diabetes. In the present study, there was a positive correlation with the time since the diagnosis of T2DM (r=0.681, *p<0.001*), when controlled for sex, suggesting that patients with a longer duration of the disease have a greater risk of these events. The positive correlations between age, time since T2DM diagnosis, and estimated CV risk underscore the progressive nature of cardiovascular risk accumulation over time in individuals with diabetes. Older individuals and those with a longer duration of diabetes exhibit a higher baseline risk for cardiovascular events, highlighting the importance of early and sustained intervention strategies to prevent or delay adverse outcomes in this vulnerable population [21]. De Jong et al. [22], in a prospective cohort study of UK Biobank participants, described that a 5-year increase in the duration of diabetes was associated with a cardiovascular risk increase of around 20%. Yao et al. [23] also reported that the duration of diabetes increases the 10-year cardiovascular risk. Thus, it seems important that the calculation of the 10-year cardiovascular risk in patients diagnosed with diabetes should consider the time of diagnosis of the disease.

The current study revealed significant differences in body weight and abdominal circumference between males and females. These findings underscore the importance of considering sex-specific

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factors in the assessment and management of metabolic syndrome among elderly individuals with diabetes. Cardiovascular risk management must consider several factors, including patient´s sex, since this will be a factor to consider in risk stratification, the therapy implemented, and the expected outcomes in terms of metabolic health [24]. Although the differences in BMI between the sexes were not statistically significant, the higher prevalence of men above the normal BMI range highlights the need for targeted interventions to address overweight and obesity and its associated cardiovascular risks in the elderly population with diabetes [25,26]. This finding could prompt a discussion on the role of BMI as a predictor of cardiovascular risk and the importance of comprehensive risk assessment beyond traditional measures. In a study that included 23,961 Chinese patients with diabetes, Hu et al. found that every 5 years of early diagnosis increased the risk of heart disease by 14%. This association was even higher in patients with obesity [27], showing that BMI should be a factor to consider when calculating cardiovascular risk.

The observed sex disparities in smoking and alcohol consumption underscore the influence of lifestyle behaviours on cardiovascular health outcomes. According to 2019 data from the National Statistics Institute, tobacco was considered the first risk factor for premature death and lost years of healthy life in Portuguese men [28]. In this national report, although the number of smokers decreased, an increase in the consumption of alcoholic beverages, compared to previous years, was observed. Smoking and alcohol consumption have a significant impact on metabolic syndrome components and cardiovascular risk, leading to the definition of intervention strategies targeting modifiable risk factors in elderly patients with diabetes [20]. The fact that tobacco and alcohol consumption habits were higher in men than women, may be an important contributor to the increased risk observed in male.

Despite the absence of significant differences between the sexes in clinical parameters such as blood pressure, cholesterol levels, and glycaemic control, it is essential to consider the cumulative impact of these factors on cardiovascular risk in elderly individuals with diabetes [24]. The finding of no significant sex differences in the prevalence of metabolic syndrome characteristics highlights the uniform burden of metabolic features among the individuals regardless of their sex.

Dyslipidaemia is a crucial factor considered within the diagnosis of metabolic syndrome, according to IDF [1], and a major factor for developing a CV disease [29]. The findings of this study suggest that while elderly patients may derive greater benefit from BP control, the effect of the intervention on LDL cholesterol may not appear as pronounced in this population. However, the impact of lowering lipid parameters in the elderly seems similar to the results observed in the prevention of CV events in younger individuals, and no additional safety concerns were found, which justifies the benefit of using lipid-lowering agents in older individuals [30]. In fact, 56.3% of the patients evaluated in this study were treated for dyslipidaemia. It is important to note that the most recent tool developed to estimate cardiovascular risk in the European general and older population, respectively Score-2 and Score-2-OP, uses the total cholesterol value as an indicator for dyslipidaemia, allowing the estimation of absolute 10-year CVD event risk reduction from risk factor treatment [29,31]. However, although diabetes was considered a predictive factor for the construction of these tools, it is not an indicator considered on their operationalization. Hence, the ADVANCE tool was selected to calculate the 10-years risk of fatal CV event in the analysed elderly population with diabetes, based on previous studies [12,32,33]. As mentioned, this calculator considers the time since diagnosis and the presence of long-term complications of diabetes, which are important factors in calculating the 10-year cardiovascular risk. Of note, although the waist circumference is a mandatory factor for the MS diagnosis according to the IDF [1], it is not considered in any CV risk calculation tool, which may be important, especially in patients with metabolic syndrome. On the other hand, scores from non-alcoholic fatty liver disease (NAFLD) scoring systems like the Fatty Liver Index (FLI), which are strongly associated with high CVD risk [34], do include waist circumference in their calculation [35]. BMI is a required parameter when calculating 10-year cardiovascular risk using the DIAbetes Lifetime perspective (DIAL) model. However, the calculator model available online indicates that this tool may underestimate the 10-year and lifetime risk without a history of

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cardiovascular disease, and that the algorithm is being calibrated [36]. Although the recalibration has already been published, the new algorithm is not yet available for online calculation [37].

HbA1c levels, reflecting the glycemic control, are associated with the reduction of non-fatal CV events, such as stroke, and microvascular and macrovascular complications [38–40]. For this reason, achieving good glycemic control is currently a recommended goal in the individualized approach to all individuals with diabetes [41]. However, the IDF criteria for diagnosing MS do not take this parameter into account, but rather fasting blood glucose [1]. Since HbA1c reflects the average of blood glucose values over the last 3 months, this could be a relevant parameter to consider for uncontrolled diabetes [42], and therefore a criterion for MS.

The results of this study show that merely effective BP control (<130 mmHg) could lead to a substantial proportion of participants (34.5%) no longer meeting the criteria for a diagnosis of MS. Furthermore, this possible intervention alone could significantly reduce the cardiovascular risk in the studied population, compared to the current risk. This highlights the potential role of aggressive risk factor modification in ameliorating metabolic abnormalities and reducing the overall burden of CV risk in diabetic groups. The fact that the calculator used (ADVANCE) does not allow the control of all the parameters considered in the CV risk calculation and/or MS, such as HbA1c, HDL cholesterol, or total cholesterol, hinders the feasibility to quantitatively calculate the impact of changes in CV risk for each individual. This would be probably a complex task, since the therapeutic objectives for some of these parameters need to be defined, considering the individual characteristics of the patient. Perhaps including even further parameters that are not covered here, such as health literacy, as previously suggested [43], could be important to reduce the CV risk.

Metabolic syndrome clustering may have an important role in the identification of priority intervention associated with cardiovascular risk, contributing to enhance the importance of early detection and intervention to mitigate adverse outcomes in this population. The burden of CV diseases attributable to metabolic risk factors has been growing during the last decades, and this trend is expected to continue, looking at the global aging and the increase in the life expectancy of the population [44].

It is important to acknowledge the limitations of the study, such as the cross-sectional design and the use of population mean for albumin creatinine ratio parameter in the risk calculation on ADVANCE calculator due to the lack of information regarding this parameter.

Future research is essential, including longitudinal studies to assess the prospective trajectory of metabolic syndrome and its relationship with cardiovascular outcomes in elderly individuals with diabetes. It would also be important to develop tools, or upgrade the existing ones, that allow the adjustment of other important modifiable parameters in the cardiovascular risk of patients with diabetes and metabolic syndrome, such as HDL cholesterol, triglycerides, fasting glucose and/or HbA1c levels.

5. Conclusions

The current study approaches the intricate relationship between metabolic syndrome, diabetes, and cardiovascular risk in the elderly population. Our findings underscore the heightened cardiovascular risk faced by individuals with diabetes and metabolic syndrome, particularly in the context of advancing age and prolonged disease duration. Sex disparities found in CV risk highlight the need for tailored interventions that address specific risk factors unique to male and female populations.

This study demonstrates the considerable potential of aggressive blood pressure control in mitigating cardiovascular risk, with notable reductions observed across the entire study cohort. The synergistic effect of combining blood pressure and LDL cholesterol interventions further emphasizes the importance of multifaceted risk reduction strategies in optimizing patient outcomes.

Further research is warranted to explore additional therapeutic approaches and modifiable factors aiming to enhance cardiovascular health in elderly patients with diabetes and metabolic syndrome.

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